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Risk of intracerebral haemorrhage with alteplase after acute ischaemic stroke: a secondary analysis of an individual patient data meta-analysis

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Summary

Background Randomised trials have shown that alteplase improves the odds of a good outcome when delivered within 4·5 h of acute ischaemic stroke. However, alteplase also increases the risk of intracerebral haemorrhage; we aimed to determine the proportional and absolute effects of alteplase on the risks of intracerebral haemorrhage, mortality, and functional impairment in different types of patients.

Methods We used individual patient data from the Stroke Thrombolysis Trialists' (STT) meta-analysis of randomised trials of alteplase versus placebo (or untreated control) in patients with acute ischaemic stroke. We prespecified assessment of three classifications of intracerebral haemorrhage: type 2 parenchymal haemorrhage within 7 days; Safe Implementation of Thrombolysis in Stroke Monitoring Study's (SITS-MOST) haemorrhage within 24–36 h (type 2 parenchymal haemorrhage with a deterioration of at least 4 points on National Institutes of Health Stroke Scale [NIHSS]); and fatal intracerebral haemorrhage within 7 days. We used logistic regression, stratified by trial, to model the log odds of intracerebral haemorrhage on allocation to alteplase, treatment delay, age, and stroke severity. We did exploratory analyses to assess mortality after intracerebral haemorrhage and examine the absolute risks of intracerebral haemorrhage in the context of functional outcome at 90–180 days.

Findings Data were available from 6756 participants in the nine trials of intravenous alteplase versus control. Alteplase increased the odds of type 2 parenchymal haemorrhage (occurring in 231 [6·8%] of 3391 patients allocated alteplase *vs* 44 [1·3%] of 3365 patients allocated control; odds ratio [OR] 5·55 [95% CI 4·01–7·70]; absolute excess 5·5% [4·6–6·4]); of SITS-MOST haemorrhage (124 [3·7%] of 3391 *vs* 19 [0·6%] of 3365; OR 6·67 [4·11–10·84]; absolute excess 3·1% [2·4–3·8]); and of fatal intracerebral haemorrhage (91 [2·7%] of 3391 *vs* 13 [0·4%] of 3365; OR 7·14 [3·98–12·79]; absolute excess 2·3% [1·7–2·9]). However defined, the proportional increase in intracerebral haemorrhage was similar irrespective of treatment delay, age, or baseline stroke severity, but the absolute excess risk of intracerebral haemorrhage increased with increasing stroke severity: for SITS-MOST intracerebral haemorrhage the absolute excess risk ranged from 1·5% (0·8–2·6%) for strokes with NIHSS 0–4 to 3·7% (2·1–6·3%) for NIHSS 22 or more (p=0·0101). For patients treated within 4·5 h, the absolute increase in the proportion (6·8% [4·0% to 9·5%]) achieving a modified Rankin Scale of 0 or 1 (excellent outcome) exceeded the absolute increase in risk of fatal intracerebral haemorrhage (2·2% [1·5% to 3·0%]) and the increased risk of any death within 90 days (0·9% [–1·4% to 3·2%]).

Interpretation Among patients given alteplase, the net outcome is predicted both by time to treatment (with faster time increasing the proportion achieving an excellent outcome) and stroke severity (with a more severe stroke increasing the absolute risk of intracerebral haemorrhage). Although, within 4·5 h of stroke, the probability of achieving an excellent outcome with alteplase treatment exceeds the risk of death, early treatment is especially important for patients with severe stroke.

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Introduction

The Stroke Thrombolysis Trialists' (STT) Collaboration has previously shown in a meta-analysis[1] of individual patient data from nine trials of alteplase versus placebo (or untreated control) that alteplase significantly improves the odds of an excellent outcome (ie, a modified Rankin Scale [mRS] of 0 or 1) when delivered within 4·5 h of the onset of ischaemic stroke. However, alteplase increases the risk of intracerebral haemorrhage within 48 h of administration,[1] and variations in the absolute risks of such haemorrhage according to clinical presentation (eg, stroke severity) might affect the long-term outcome. In the past 2 years, several publications have drawn attention to the scarcity of reliable information about the hazards of alteplase and how they relate to benefits in different groups of patients, particularly patients presenting later than 3 h after stroke

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Research in context

Evidence before this study

Meta-analyses have previously shown that alteplase increases the risk of intracerebral haemorrhage, but the extent to which the absolute excess risk differs by haemorrhage type, stroke severity, age, or treatment delay was uncertain, as was the balance between the risk of intracerebral haemorrhage and treatment benefit in different patients. We used individual participant data from the Stroke Thrombolysis Trialists' (STT) meta-analysis of nine trials of alteplase versus control to do secondary analyses of the available evidence.

Added value of this study

This study provides estimates of symptomatic intracerebral haemorrhage risk, and benefits due to alteplase, in patients grouped by stroke severity, age, and treatment delay. With the individual participant data, we were able to adjust for complex intercorrelations between variables to produce reliable estimates of absolute treatment effects.

Implications of all the available evidence

The absolute benefits of alteplase decrease with treatment delay, and the absolute harms due to alteplase (from intracranial haemorrhage) increase with stroke severity. When delivered within 4·5 h, the proportion of patients with a good outcome exceeds that of patients dying from intracranial haemorrhage. However, because the risk of haemorrhage is highest in patients with the most severe stroke, prompt treatment of these patients is important. These absolute risk estimates will be useful to communicate the effects of alteplase to patients, families, and clinicians.

onset.[2,3] In the UK, the Medicines and Healthcare Products Regulatory Agency Expert Working Group considered both the STT Collaboration's published analyses and, in confidence, unpublished analyses of the effects of alteplase on intracerebral haemorrhage as part of its review of the market authorisation for alteplase in acute ischaemic stroke.[4]

Because strong associations exist between prognostic variables in the trials included in the STT database (eg, patients treated earlier tended to be older and to have had more severe strokes), an assessment of benefit and harm can only be done reliably using multivariable models applied to individual participant data. The STT's protocol[5] outlined secondary analyses that were to be done in addition to the main analysis.[1] The aim of this Article is to describe the results of secondary analyses assessing the proportional and absolute effects of alteplase on the risk of intracerebral haemorrhage, mortality, and functional impairment in patients with different characteristics. We also explore how such variations might affect the net effects of alteplase by 90–180 days after stroke.

Methods

Study design

The methods for the meta-analysis planned by the Stroke Thrombolysis Trialists' (STT) Collaboration have been described in detail in the protocol[5] and in the main report of the primary analysis.[1] Briefly, we sought individual patient data from all completed randomised phase 3 trials of intravenous alteplase in patients with acute ischaemic stroke. We identified potentially eligible trials for our analysis from a systematic review[6] of trials of thrombolysis that had been updated in 2013 and from active trialists and the manufacturer of alteplase used in all participating trials (Boehringer Ingelheim, Ingelheim, Germany).[5] We analysed participants in the group to which they were randomly assigned (intention to treat).

Outcomes

The main outcome of interest in this secondary analysis was intracerebral haemorrhage, which was defined in three ways: type 2 parenchymal haemorrhage by 7 days after randomisation; Safe Implementation of Thrombolysis in Stroke Monitoring Study's (SITS-MOST) haemorrhage;[7] or fatal intracerebral haemorrhage within 7 days.

Type 2 parenchymal haemorrhage by 7 days after randomisation was defined as dense blood clots exceeding 30% of the infarct volume with a significant space-occupying effect seen on brain imaging, whether within or remote from the infarct.[8] For patients from the Third International Stroke Trial (IST-3),[9] in which type 2 parenchymal haemorrhage defined solely on radiological findings was not a prespecified secondary outcome, we recorded a type 2 parenchymal haemorrhage if there was a report from the IST-3 blinded CT-reading panel of significant brain parenchymal haemorrhage, local or remote from the infarct, or significant diffuse haemorrhagic transformation of an infarct on brain imaging.

SITS-MOST haemorrhage[7] was defined as type 2 parenchymal haemorrhage on imaging with an increase in the National Institutes of Health Stroke Scale (NIHSS) of 4 points or more from baseline (or the lowest point in the first 24 h) or that led to death within 36 h of treatment. In IST-3, we approximated the SITS-MOST definition by the occurrence within 24 h of clinically significant deterioration or death, together with evidence of either significant brain parenchymal haemorrhage (local or distant from the infarct) or significant haemorrhagic transformation of an infarct on brain imaging, which, in the judgment of the blinded adjudication panel, was likely to have worsened mass effect or contributed to the burden of brain damage.[9]

Fatal intracerebral haemorrhage was defined as type 2 parenchymal haemorrhage (or its approximation in IST-3) confirmed with imaging (or at autopsy) and death within 7 days of randomisation.

The timing of brain imaging to detect intracerebral haemorrhage varied slightly across the participating trials. The protocol of each trial mandated imaging at about 24 h after randomisation and additional brain imaging if neurological deterioration occurred. Further routine brain imaging was done at 3–5 days in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET);[10] at 1 week in the National Institutes of Neurological Diseases and Stroke (NINDS) A and B[11] and in the European Cooperative Acute Stroke Study (ECASS) I, II, and III;[8,12,13] and at 23–37 days in the Alteplase Thrombolysis for Acute Non-interventional Therapy in Ischemic Stroke (ATLANTIS) A and B.[14,15]

Analyses of the effect of alteplase on death from all causes within 90 days, both overall and when separated by a period of follow-up and treatment delay, have been published previously.[1] In post-hoc analyses of mortality for this analysis, we subdivided deaths into those that were preceded by clinically significant intracerebral haemorrhage (defined as fatal intracerebral haemorrhage within 7 days or death following SITS-MOST haemorrhage) and all other deaths.

We analysed the mRS to define stroke outcome at 3–6 months. We defined an excellent stroke outcome as mRS of 0–1 (ie, symptom free or residual symptoms with no loss of activity) and a very poor stroke outcome as mRS of 5–6 (ie, bed bound or dead) at 3–6 months. In IST-3, mRS was reported at 6 months rather than 3 months. Therefore, for consistency between the previously published analyses of 90 day mortality and the odds ratios (OR) for mRS 0–5 versus 6 in this analysis, we made the assumption that IST-3 patients who died between 91 days and 6 months (125 [4%] of 3035 IST-3 participants) had an mRS of 5 at 90 days.[1]

Statistical analysis

We used logistic regression, stratified by trial, to model the common linear dependence of the log odds of intracerebral haemorrhage on treatment allocation (alteplase or control), treatment delay, age, baseline

	NINDS A[11]	NINDS B[11]	ECASS I[8]	ECASS II[12]	ATLANTIS A[15]	ATLANTIS B[14]	ECASS III[13]	EPITHET[10]	IST-3[9]	Total
Patients	291	333	620	800	142	613	821	101	3035	6756
Alteplase	144 (49%)	168 (50%)	313 (50%)	409 (51%)	71 (50%)	301 (49%)	418 (51%)	52 (51%)	1515 (50%)	3391 (50%)
Control	147 (51%)	165 (50%)	307 (50%)	391 (49%)	71 (50%)	312 (51%)	403 (49%)	49 (49%)	1520 (50%)	3365 (50%)
Treatment delay (h)	2·0 (0·6)	2·0 (0·6)	4·4 (1·1)	4·3 (1·1)	4·3 (1·1)	4·4 (0·8)	4·0 (0·4)	4·9 (0·8)	4·2 (1·2)	4·0 (1·2)
>0 to ≤3	290 (>99%)	333 (100%)	87 (14%)	158 (20%)	22 (15%)	39 (6%)	..	..	620 (20%)	1549 (23%)
>3 to ≤4·5	1 (<1%)	..	233 (38%)	265 (33%)	53 (37%)	249 (41%)	788 (96%)	31 (31%)	1148 (38%)	2768 (41%)
>4·5	..	..	295 (48%)	370 (46%)	67 (47%)	321 (52%)	6 (1%)	69 (68%)	1266 (42%)	2394 (35%)
Missing	..	..	5 (1%)	7 (1%)	..	4 (1%)	27 (3%)	1 (1%)	1 (<1%)	45 (1%)
Age (years)	66 (11)	68 (12)	65 (12)	66 (11)	66 (13)	66 (11)	65 (12)	72 (13)	77 (12)	71 (13)
≤80	279 (96%)	289 (87%)	615 (>99%)	792 (99%)	142 (100%)	608 (>99%)	805 (98%)	76 (75%)	1418 (47%)	5024 (74%)
>80	12 (4%)	44 (13%)	5 (1%)	8 (1%)	..	3 (<1%)	15 (2%)	25 (25%)	1617 (53%)	1729 (26%)
Missing	..	..	..	..	..	2 (<1%)	1 (<1%)	..	..	3 (<1%)
Stroke severity (NIHSS)	14 (7)	15 (7)	12 (6)	12 (6)	13 (7)	11 (6)	10 (5)	13 (6)	12 (7)	12 (7)
>0 to ≤4	16 (5%)	13 (4%)	34 (5%)	47 (6%)	10 (7%)	47 (8%)	98 (12%)	1 (1%)	400 (13%)	666 (10%)
>4 to ≤10	78 (27%)	98 (29%)	189 (30%)	339 (42%)	57 (40%)	279 (46%)	389 (47%)	40 (40%)	1064 (35%)	2533 (37%)
>10 to ≤15	68 (23%)	63 (19%)	183 (30%)	232 (29%)	28 (20%)	128 (21%)	163 (20%)	22 (22%)	601 (20%)	1488 (22%)
>15 to ≤21	76 (26%)	78 (23%)	146 (24%)	113 (14%)	25 (18%)	106 (17%)	142 (17%)	29 (29%)	618 (20%)	1333 (20%)
>21	45 (15%)	74 (22%)	28 (5%)	43 (5%)	20 (14%)	33 (5%)	18 (2%)	9 (9%)	352 (12%)	622 (9%)
Missing	8 (3%)	7 (2%)	40 (6%)	26 (3%)	2 (1%)	20 (3%)	11 (1%)	..	..*	114 (2%)
Women	120 (41%)	142 (43%)	231 (37%)	331 (41%)	45 (32%)	250 (41%)	325 (40%)	43 (43%)	1570 (52%)	3057 (45%)
History of hypertension	188 (65%)	220 (66%)	258 (42%)	412 (52%)	87 (61%)	364 (59%)	514 (63%)	71 (70%)	1954 (64%)	4068 (60%)
History of stroke	49 (17%)	34 (10%)	83 (13%)	158 (20%)	31 (22%)	89 (15%)	89 (11%)	11 (11%)	699 (23%)	1243 (18%)
History of diabetes mellitus	64 (22%)	67 (20%)	81 (13%)	169 (21%)	27 (19%)	130 (21%)	129 (16%)	23 (23%)	388 (13%)	1078 (16%)
History of atrial fibrillation	55 (19%)	60 (18%)	113 (18%)	188 (24%)	37 (26%)	97 (16%)	108 (13%)	42 (42%)	914 (30%)	1614 (24%)
Antiplatelet use	78 (27%)	93 (28%)	87 (14%)	196 (25%)	59 (42%)	211 (34%)	201 (24%)	30 (30%)	1306 (43%)	2261 (33%)
Weight (kg)	78 (17)	78 (19)	74 (12)	75 (14)	80 (20)	79 (18)	78 (15)	75 (19)	72 (15)	75 (16)
Systolic blood pressure (mm Hg)	154 (21)	152 (21)	154 (23)	152 (21)	152 (24)	152 (21)	153 (21)	148 (19)	155 (24)	154 (22)
Diastolic blood pressure (mm Hg)	85 (13)	85 (14)	87 (13)	84 (13)	81 (14)	82 (14)	84 (14)	78 (13)	82 (15)	83 (14)

Data are n (%) or mean (SD). NINDS=National Institute of Neurological Disorders and Stroke. ECASS=European Cooperative Acute Stroke Study. ATLANTIS=Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. EPITHET=Echoplanar Imaging Thrombolytic Evaluation Trial. IST=International Stroke Trial. NIHSS=National Institutes of Health Stroke Scale. *In IST-3, 244 patients had their baseline NIHSS score predicted from other measurements recorded at their baseline assessment. With exclusion of these patients, the numbers of IST-3 patients in each NIHSS categories would be 385, 972, 531, 559, and 344, respectively.

Table 1: **Baseline characteristics of patients in participating trials**

stroke severity (measured with the NIHSS), and interactions between treatment allocation and each of these other baseline covariates. Treatment delay, age, and stroke severity were all analysed as linear variables. In addition to such continuous analyses, we also used regression models that analysed each baseline covariate in predefined categories of treatment delay (≤3·0 h, >3 to ≤4·5 h, and >4·5 h), age (≤80 years and >80 years), and stroke severity (NIHSS ≤4, 5–10, 11–15, 16–21, and ≥22). We imputed missing 6 month mRS data in IST-3 from 7 day assessments with an algorithm that worked well in patients who had both measurements.[5] We assessed whether treatment delay, age, stroke severity, or trial modified (individually or jointly) the overall effect of alteplase on particular outcomes on the basis of the significance of the relevant treatment interactions in the likelihood ratio tests (ie, through comparison of minus twice the log-likelihood statistic between appropriate nested models). We used trial-by-treatment interactions to assess whether important differences in the odds of intracerebral haemorrhage with alteplase existed between the nine trials, and between IST-3 (with untreated-control) and the other (placebo-controlled) trials combined.

We calculated Kaplan-Meier cumulative mortality curves during the first 90 days for patients allocated to the alteplase and control groups (crudely pooling across all trials). Subsequently, we used trial-stratified Cox regression to estimate the mortality hazard ratio [HR] within 90 days for deaths preceded by clinically significant intracerebral haemorrhage and for all other deaths, with the time to event either at death, or censored at 90 days.

Stroke severity and treatment delay are both important determinants of stroke outcome for patients given alteplase. However, stroke severity and treatment delay were correlated in the included trials.[1] Therefore, to prevent treatment delay from confounding the observed mRS distribution when treated patients were subdivided by their baseline stroke severity (NIHSS ≤4, 5–10, 11–15, 16–21, and ≥22), we compared, for each baseline NIHSS group, the observed mRS distribution for control patients with the expected distribution if given alteplase within 3 h or within 4·5 h. We obtained this expected distribution by applying the overall ORs for each mRS dichotomy (ie, mRS 0 *vs* 1–6 and mRS 0–1 *vs* 2–6) within a given time window (≤4·5 h, <3 h, or 3–4·5 h) to the observed mRS

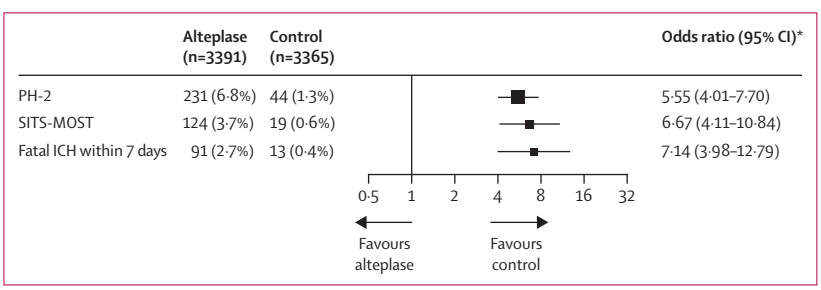

***Figure 1*: Effect of alteplase treatment within 7 days on type 2 parenchymal haemorrhage, SITS-MOST haemorrhage, and fatal intracerebral haemorrhage**

ICH=intracerebral haemorrhage. PH-2=parenchymal haemorrhage type 2. SITS-MOST=Safe Implementation of Thrombolysis in Stroke Monitoring Study. *Estimated from a trial-stratified logistic regression model adjusted only for treatment allocation.

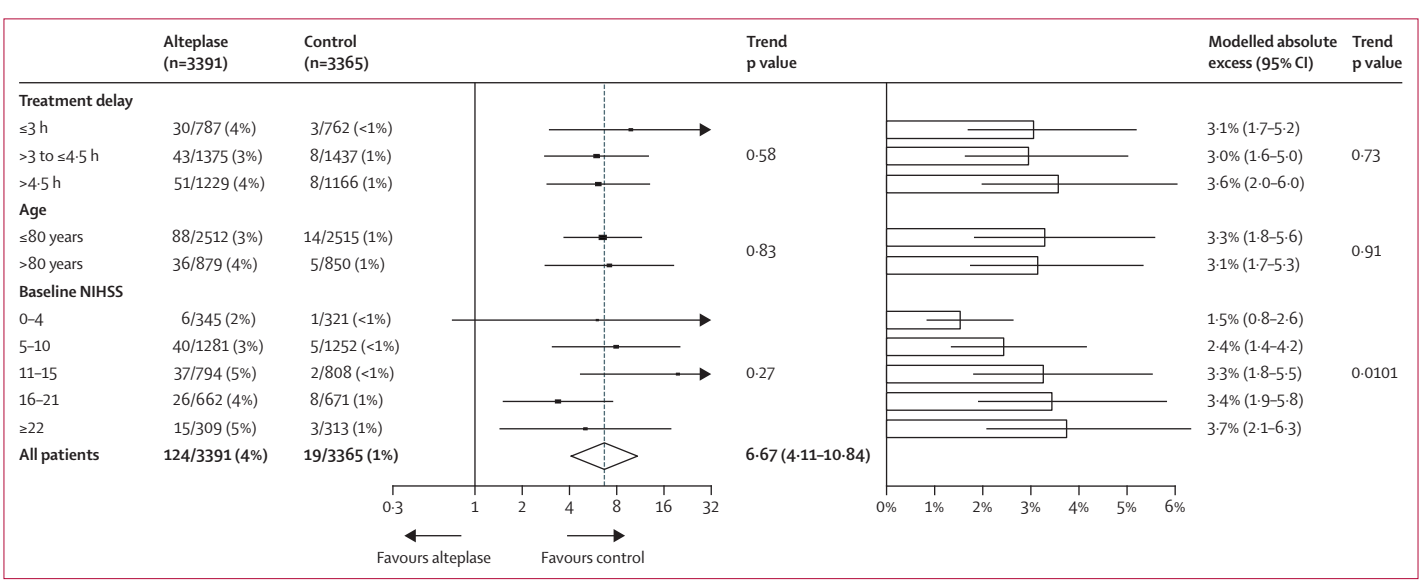

***Figure 2*: Effect of alteplase on SITS-MOST intracerebral haemorrhage at 24–36 h by time to treatment, age, and stroke severity**

For each of the three baseline characteristics shown, the OR subgroup estimates are derived from a single trial-stratified logistic regression model that allows for separate estimation of the OR in each of the subgroups after adjustment for the other two baseline characteristics (but not possible interactions with those characteristics). The overall effect (indicated by the open diamond) is the trial-stratified logistic regression estimate adjusted only for treatment allocation. The absolute excess risk (95% CI) for each subgroup is estimated by application of the OR seen among all randomly assigned patients (or its confidence limits) to the mean expected risk in control-allocated patients for that subgroup (estimated from a logistic regression model among all participants adjusted for trial, treatment allocation, the subgroup of interest, and mean levels of the other two baseline characteristics). SITS-MOST=Safe Implementation of Thrombolysis in Stroke Monitoring Study. OR=odds ratio. NIHSS=National Institutes of Health Stroke Scale.

distribution at 3–6 months in control-allocated patients. Similarly, the estimates of absolute excess risk subdivided by a given characteristic (treatment delay, age, or stroke severity) were obtained by applying the overall OR estimates (and their 95% CIs) to the control rates that would have been expected for that subgroup had the mean levels of the other two characteristics applied.

All estimates of treatment effect are provided with their 95% CIs with p values that are deemed conventionally significant, without allowance for multiple testing, at the 5% significance level. We did the analyses with SAS (version 9.3) and R (version 2.11.1).

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The secretariat had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Data were available from 6756 participants in nine trials of intravenous alteplase versus control (table). Baseline data on treatment delay, age, and NIHSS were complete for almost all participants (6602 (98%) of 6756 participants). Individual participant data were sought from an additional five trials[16–20] involving 270 participants, which reported a total of 18 patients with intracerebral haemorrhage (11 patients received alteplase and seven from the control), but were either not available or, in one case,[18] the authors could not be contacted.

Overall, 275 (4·1%) of 6756 participants had a type 2 parenchymal haemorrhage within 7 days of treatment, of which 104 (38%) were fatal within 7 days (91 [39%] of 231 participants in the alteplase group *vs* 13 [30%] of 44 in the control group). 143 (52%) of these haemorrhages were SITS-MOST haemorrhages (50 [40%] of 124 *vs* nine [47%] of 19), of which 59 (41%) were fatal within 7 days. Alteplase increased the odds of intracerebral haemorrhage by a factor of about six to seven, depending on the definition used: type 2 parenchymal haemorrhage (231 [6·8%] of 3391 *vs* 44 [1·3%] of 3365; OR 5·55, 95% CI 4·01–7·70; absolute excess 5·5% [4·6–6·4]); SITS-MOST haemorrhage (124 [3·7%] of 3391 *vs* 19 [0·6%] of 3365; OR 6·67, 4·11–10·84; absolute excess 3·1% [2·4–3·8]); and fatal intracerebral haemorrhage within 7 days (91 [2·7%] of 3391 *vs* 13 [0·4%] of 3365; OR 7·14, 3·98–12·79; absolute excess 2·3% [1·7–2·9%]; figure 1). These ORs were similar after adjusting for baseline variables (age, sex, treatment delay, stroke severity, previous stroke, or transient ischaemic attack, previous diabetes, antiplatelet use, weight, and systolic blood pressure at randomisation; data not shown). We found no evidence that the ORs for any of the definitions of intracerebral haemorrhage differed between trials, or between IST-3 (which was untreated control) and the eight placebo-controlled trials (all heterogeneity p values >0·05; appendix p 2). The proportion of patients with type 2 parenchymal haemorrhage who died by 7 days was also similar in IST-3 (62 [39%] of 159 patients) and in the other eight placebo-controlled trials (42 [36%] of 116).

For each type of intracerebral haemorrhage, the proportional effects of alteplase were similar irrespective of time to treatment, age, or stroke severity (appendix pp 3–5; all p values for interaction >0·05). The estimated absolute excess risks were similar irrespective of time to treatment and age, but increased with increasing stroke severity for type 2 parenchymal haemorrhage (p<0·0001; appendix p 6), fatal intracerebral haemorrhage (p=0·0002; appendix p 7), and SITS-MOST haemorrhage (p=0·0101; figure 2). For SITS-MOST intracerebral haemorrhages (ie, clinically significant bleeds in which there was both radiological evidence of bleeding and worsening symptoms within 36 h of treatment), the absolute excess risk over control increased from 1·5% (95% CI 0·8–2·6%) in patients with mild strokes (baseline NIHSS 0–4) to 3·7% (2·1–6·3%) in patients with the most severe strokes (NIHSS ≥22; figure 2).

Cause of death was not widely available in participating trials, but we did exploratory analyses to assess the risk of death preceded by clinically significant intracerebral haemorrhage and of all other deaths at 90 days. Among all trial participants, allocation to alteplase (*vs* control) was

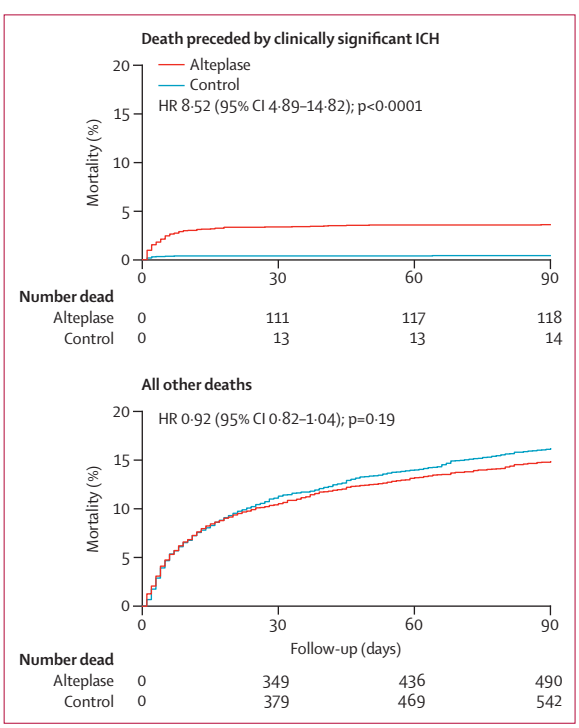

***Figure 3*: The effect of alteplase on deaths after clinically significant ICH,* and all other deaths, within 90 days**

Hazard ratio (HR) estimated by Cox proportional hazards regression stratified by trial, with adjustment for treatment allocation. ICH=intracerebral haemorrhage. SITS-MOST=Safe Implementation of Thrombolysis in Stroke Monitoring Study. *Fatal haemorrhage within 7 days or death after SITS-MOST haemorrhage.

See Online for appendix

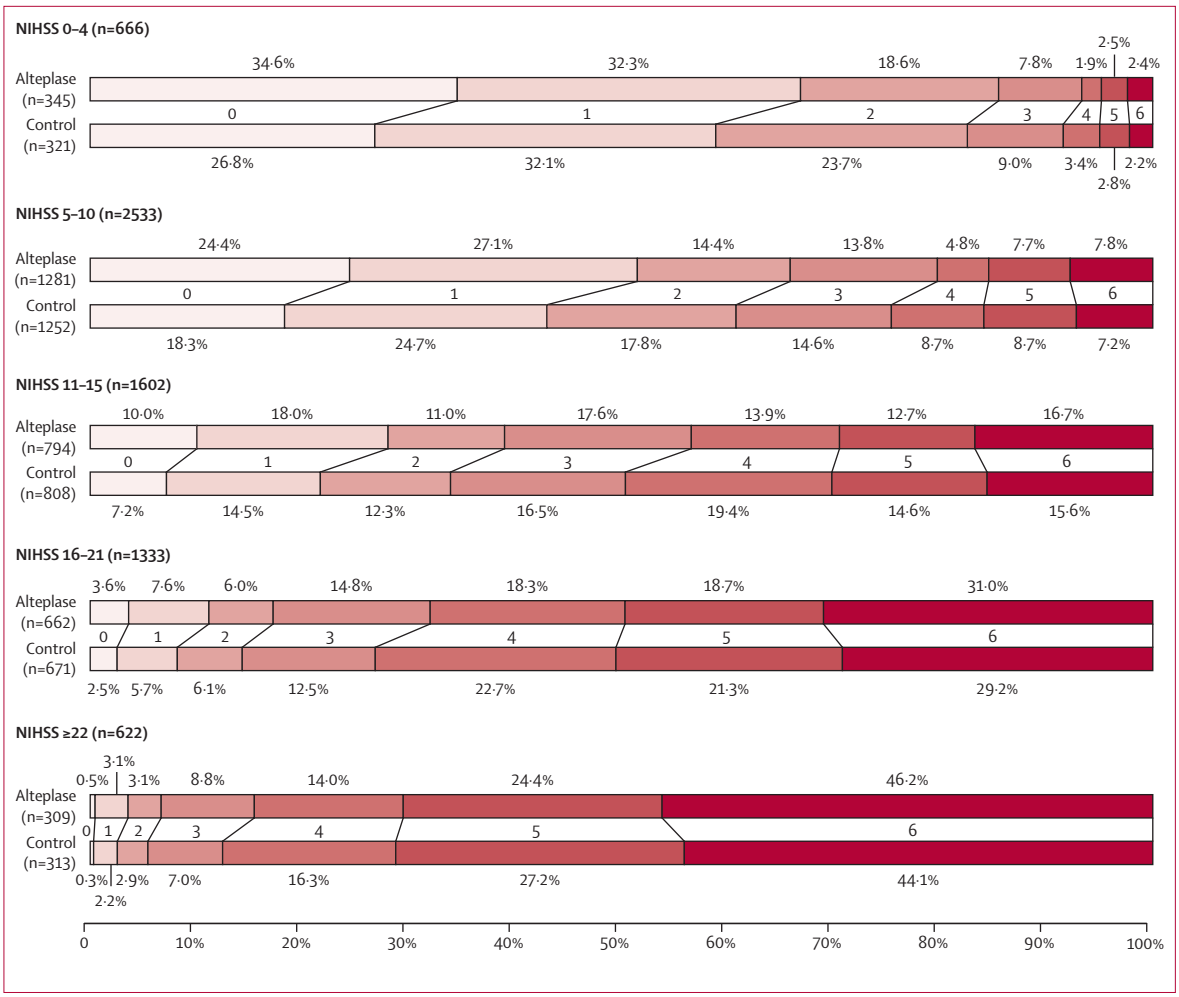

Figure 4: **Estimated proportion of patients in each mRS score category with or without alteplase, according to stroke severity at baseline**
An mRS of 0–1 indicates an excellent outcome: survival symptom free or with residual symptoms with no loss of activity. mRS 5–6 indicates bed bound or dead at 3–6 months. In IST-3, 125 (4·1%) of 3035 patients died between 3 and 6 months. For comparability of mRS 6 between IST-3 and the other trials (which assessed mRS scores at 3 months), these patients were reassigned an mRS of 5 for this analysis. NIHSS=National Institutes of Health Stroke Scale. mRS=modified Rankin Scale. IST-3=Third International Stroke Trial.

associated with a significant increase in the risk of death preceded by clinically significant intracerebral haemorrhage within 90 days (118 [3·5%] of 3391 *vs* 14 [0·4%] of 3365; HR 8·52, 95% CI 4·89–14·82; figure 3). However, deaths were offset by non-significantly fewer deaths among people who had not had a haemorrhage (490 [14·5%] of 3391 *vs* 542 [16·1%] of 3365; HR 0·92, 0·82–1·04; figure 3). An analysis that defined clinically significant haemorrhage by the radiological appearance of a type 2 parenchymal haemorrhage, rather than by the SITS-MOST definition, gave similar results (appendix p 10).

Because the estimated absolute excess risk of intracerebral haemorrhage increased according to the five baseline categories of stroke severity, we assessed the effect of this increase on the expected distribution of mRS scores at 90 days in all patients treated within 4·5 h (mean, at 3 h and 20 min) by applying the OR for each mRS transition to the control population (figure 4). Among patients with the mildest strokes (NIHSS 0–4), alteplase within 4·5 h would be expected to result in an absolute increase in excellent outcome of 8·0% (95% CI 4·5 to 11·1), and to reduce the absolute risk of very poor outcome by 0·1% (–0·6 to 0·8; consisting of a 0·3% absolute reduction in severe disability [mRS 5] and a 0·2% absolute increase in death). For the most severe strokes (NIHSS ≥22), alteplase would be expected to result in an absolute increase in excellent outcome of 1·0% (0·5 to 1·5), and to reduce the absolute risk of very poor outcome by 0·6% (–2·3 to 4·1; consisting of a 2·8% reduction in severe disability and a 2·1% absolute increase in death. Overall, for patients treated within 4·5 h, the absolute increase in the proportion of patients achieving a modified Rankin Scale of 0 or 1 (6·8%, 4·0 to 9·5) exceeded the absolute increase in risk of fatal intracerebral haemorrhage (2·2%,

1·5 to 3·0) and the absolute increased risk of death within 90 days (0·9%, –1·4 to 3·2).

Discussion

In the nine trials included in the analysis, alteplase increased the odds of intracerebral haemorrhage within the first 7 days by about six to seven times compared with control treatment. The proportional increase in the odds was similar irrespective of treatment delay, age, and stroke severity at baseline. In these trials, the underlying risk of intracerebral haemorrhage without alteplase increased with stroke severity, which is consistent with a systematic review of 55 observational studies in which each 1 point increment in the NIHSS was associated with an 8% (95% CI 6–11) increase in the odds of intracerebral haemorrhage (p<0·001).[21] In the absence of heterogeneity of the OR for haemorrhage, the absolute excess risk of intracerebral haemorrhage was higher in patients with the severest strokes. Overall, alteplase resulted in a 2·3% absolute excess of fatal intracerebral haemorrhage during the first week (figure 1). After the first week, deaths preceded by intracerebral haemorrhage remained elevated in patients given alteplase (figure 3), perhaps because of disorders associated with chronic immobility (eg, pneumonia). By contrast, during the first 90 days, non-significantly fewer other deaths occurred in patients in the alteplase group than in the control group, perhaps because of the beneficial effects of alteplase on functional outcome (figures 3, 4).

Taken together, the present analyses and our previous report[1] show that, when given within 4·5 h, alteplase is associated with an early hazard due to intracerebral haemorrhage but a later benefit in terms of less disability. This study raises the hypothesis that alteplase reduces mortality risk in patients in whom it does not cause intracerebral haemorrhage. This pattern is analogous to that of many surgical procedures (eg, carotid endarterectomy) that are associated with an early hazard followed by a later survival benefit,[22,23] and for which the balance of hazard and benefit in particular types of patients determines their net clinical outcome.

The net effects of alteplase in particular types of patients are best represented by the predicted shift in the distribution of the mRS in patients allocated to alteplase or control. Our previous analyses showed that the benefits of alteplase diminish with increasing treatment delay, whereas the present analyses suggest that the absolute excess risk of intracerebral haemorrhage increases with stroke severity. Our exploratory analyses suggest that these two variables help determine the net effects of alteplase in particular patients. These variables might help to explain the non-significantly larger relative increase in 90 day mortality in patients treated later than 3 h in our previous report.[1] The patterns could be due to the shifting balance between an early increase in mortality from intracerebral haemorrhage (which is of similar magnitude irrespective of delay) and a reduced mortality due to salvaged brain tissue in patients treated early, with the magnitude of this benefit diminishing as delay increases (ie, time is brain).

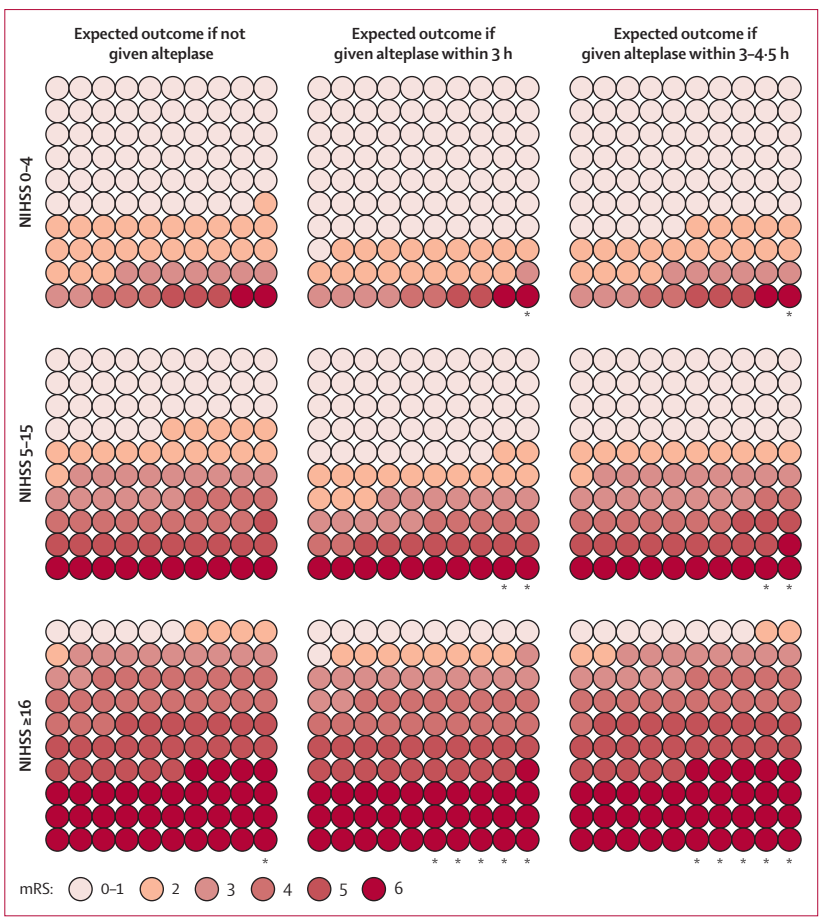

***Figure 5*: Expected stroke outcome at 3–6 months for different groups of patients**
mRS 0–1 indicates an excellent outcome: survival symptom free or residual symptoms with no loss of activity. mRS 5–6 indicates bed bound or dead at 3–6 months. Each 10×10 grid represents 100 hypothetical patients who have had a stroke with severity 0–4 NIHSS points, 5–15 points, or 16 or more points. mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. *Death within 7 days and after a type 2 parenchymal haemorrhage.

There is a need for improved representations of the benefits and risks of alteplase, building on those developed previously,[24–27] to better equip clinicians in discussions with patients and their family members. Established approaches of representing mRS (figure 4) have the inherent limitation that they do not directly represent the additional risks of fatal intracerebral haemorrhage. Figure 5 is an example of a possible representation of the expected effects of alteplase on the distribution of mRS scores, subdivided by stroke severity.

The results of previous trials have shown that intra-arterial thrombectomy, when given to patients who have already received intravenous thrombolysis, leads to improved outcomes[28–32] in patients with large artery ischaemic stroke and documented proximal arterial occlusion. This combination might help to improve the ratio of benefit to risk by magnifying benefit through

improved salvage of brain tissue. Alternatively, this ratio might be improved by reducing the risk of intracerebral haemorrhage with intravenous thrombolytic therapy—eg, by use of tenecteplase as an alternative to alteplase,[33,34] use of a reduced dose of alteplase (0·6 mg/kg),[35] or by targeting thrombolysis on the basis of neuroimaging appearances.[36,37]

Although our analyses provide a general guide to the effects of alteplase in different types of patients, our study had several limitations. First, and most importantly, despite having access to individual participant data from nine trials in almost 7000 patients with acute ischaemic stroke, the number of outcomes with which to examine treatment effects in different patient subgroups was small.[38] Although we recognise the need to provide improved information for doctors and patients, we believe that treatment decisions need to take account of both statistical uncertainty and the possibility that different patients and their families might reach different decisions when presented with the same data on expected outcomes. The second limitation was that the methods used by IST-3 differed in several respects to those of the other trials. IST-3 did not have a placebo control, which increased the potential for biased reporting; for example, a greater tendency to investigate possible intracerebral haemorrhage in the alteplase group than in the control group. However, alteplase increased the odds of intracerebral haemorrhage to a similar extent in IST-3 and the other trials (appendix), suggesting that any bias due to the open nature of IST-3 was small. IST-3 also did not record type 2 parenchymal or SITS-MOST haemorrhages, but defined equivalent categories. In the future, any such limitations caused by different symptomatic haemorrhage definitions and classifications could be mitigated by the use of the Heidelberg classification of intracerebral bleeding events.[39]

A third limitation was that we did not have data on cause of death available, but could only examine the effects of alteplase on deaths that followed a haemorrhage. However, our data strongly suggest that most early deaths after a type 2 parenchymal haemorrhage were likely to be due to the haemorrhage. In particular, the increased risk of death from any cause by 7 days (absolute excess 2·2%)[1] is almost identical to the increased risk of fatal ICH within 7 days (2·3%; figure 1). Additionally, death preceded by clinically significant haemorrhage remained elevated after the first week (figure 3). The most likely explanation for these observations is that haemorrhage led to death in almost all such cases (either directly or after withdrawal of medical intervention), because the alternative explanation—that patients given alteplase were at least seven times more likely than control patients to die from causes unrelated to the bleed—seems highly implausible in view of their similar prognostic scores at randomisation and the absence of any other known hazard of alteplase.

Finally, we were restricted in the extent to which we could assess the effect of other potential risk factors, such as blood glucose and blood pressure control, that have previously been associated with increased bleeding risk after alteplase administration, and we could not assess the effects of alteplase on less severe intracerebral haemorrhage because the requisite data were not consistently available.

Although alteplase increases the early risk of haemorrhagic stroke, when given within 4·5 h of acute ischaemic stroke the increased proportion of patients with an excellent outcome exceeded the increased proportion dying from intracerebral haemorrhage. The greatest absolute risk of intracerebral haemorrhage after alteplase was in patients with the most severe strokes, among whom prompt treatment is essential to achieve benefit.

Contributors

WH and EB had the original idea for this meta-analysis and implemented data definitions in 2004. KRL and EB refined the approach in 2010. CB, PS, and JW had the idea for this secondary analysis of the meta-analysis and all authors contributed to the subsequent study protocol and statistical analysis plan. All authors contributed either to the acquisition of the original trial data or the creation of the combined dataset. JE and LB did the statistical analysis. WNW wrote the first draft of the report. All authors contributed to the interpretation of the results, revision of the report, and have approved the final version of the manuscript.

Stroke Thrombolysis Trialists

Collaborators ATLANTIS A and B (GA, JG, MGL, JMO); ECASS-1, ECASS-2, and ECASS-3 (EB, WH, MKa, KRL, RvK, DT, NW); EPITHET (SD, GD, MP); IST-3 (PS, JW, RIL, GC, WNW); and NINDS A and B (TB, JG, PL). *Statistical Analysis Centre and Secretariat* CB, LB, EB, Kelly Davies, JE, Heather Halls, Lisa Holland, GH, Clare Mathews, Samantha Smith, and Kate Wilson.

Declaration of interests

CB and JE have not accepted fees, honoraria, or paid consultancies but are involved in clinical trials funded by Merck, Novartis, and Pfizer, and the University of Oxford was the trial sponsor in all cases. KRL has received speaker fees from and has served on the data monitoring committee of trials for Boehringer Ingelheim, and his department has received research grant support from Genentech. GA has received research grant support from Lundbeck; fees for consultancy and advisory board membership from Lundbeck, Covidien, Codman, and Genentech; and fees for acting as an expert witness; and owns stock in iSchemaView. EB is employed by Boehringer Ingelheim. SD has received honoraria from Boehringer Ingelheim, EVER Pharma, and Sanofi, and has received fees for consultancy and advisory board membership from Boehringer Ingelheim and Sanofi. GD has received research grant support from the NHMRC (Australia) and honoraria from Pfizer, Bristol-Myers Squibb, AstraZeneca, Boehringer Ingelheim, and Merck Sharp & Dohme. JG has received fees for consultancy and advisory board membership from Lundbeck. RvK has received speaker fees and honoraria from Penumbra and Lundbeck. RIL has received honoraria from Boehringer Ingelheim and Covidien. JMO has received consultancy and speaker fees from Boehringer Ingelheim, AstraZeneca, Servier, Boston Scientific, and Bristol-Myers Squibb. MP has received travel support from Boehringer Ingelheim. DT has received speaker fees and fees for consultancy and advisory board membership from Boehringer Ingelheim and Bayer. KT has received research grant support from the Ministry of Health, Labour, and Welfare of Japan, and speaker fees from Mitsubishi Tanabe Pharma. JW has received research grant support from the UK Medical Research Council. NW's institution has received research grants from Boehringer Ingelheim, Covidien, Stryker, and Codman. WNW has received research grant support from the UK Medical Research Council. PS has received honoraria for lectures, which were paid to the department from Boehringer Ingelheim. WH has received research grant support from Boehringer Ingelheim, and speaker fees and fees for consultancy and advisory board membership from Boehringer Ingelheim. LB, PL, TB, GC, GH, MKa, MKo, MGL, NW, and GJdZ declare no competing interests.

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